

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 13 DEC 2005

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Applicant's or agent's file reference	FOR FURTHER ACTION	
	See Form PCT/IPEA/416	
International application No. PCT/IB2004/002078	International filing date (day/month/year) 21.06.2004	Priority date (day/month/year) 01.07.2003
International Patent Classification (IPC) or national classification and IPC C07J1/00		
Applicant PHARMACIA & UPJOHN COMPANY et al ✓		

<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> (sent to the applicant and to the International Bureau) a total of sheets, as follows:</p> <ul style="list-style-type: none"> <input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). <input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>
<p>4. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Box No. I Basis of the opinion <input type="checkbox"/> Box No. II Priority <input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability <input type="checkbox"/> Box No. IV Lack of unity of invention <input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement <input type="checkbox"/> Box No. VI Certain documents cited <input type="checkbox"/> Box No. VII Certain defects in the international application <input type="checkbox"/> Box No. VIII Certain observations on the international application

Date of submission of the demand 11.08.2004 ✓	Date of completion of this report 12.12.2005
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Samsam Bakhtiary, M Telephone No. +49 89 2399-8556



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/IB2004/002078

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
 - This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
 - international search (under Rules 12.3 and 23.1(b))
 - publication of the international application (under Rule 12.4)
 - international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

Description, Pages

1-14 as originally filed

Claims, Numbers

1-7 as originally filed

a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. The amendments have resulted in the cancellation of:
 - the description, pages
 - the claims, Nos.
 - the drawings, sheets/figs
 - the sequence listing (*specify*):
 - any table(s) related to sequence listing (*specify*):
4. This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - the description, pages
 - the claims, Nos.
 - the drawings, sheets/figs
 - the sequence listing (*specify*):
 - any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/IB2004/002078

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-7
	No:	Claims	1
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-7
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

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**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/IB2004/002078

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Reference is made to the following documents:

- D1: MADYASHTA, K.M.: "transformation of dehydroepiandrosterone and pregnenolone by mucor piriformis" APPL. MICROBIOL. BIOTECHNOL., vol. 44, 1995, pages 339-343, XP002293813
- D2: BENASSON, C.M.: "the hydroxylation of androstenes by cephalopodium aphidicola" PHYTOCHEMISTRY, vol. 49, no. 8, 1998, pages 2355-2358, XP002293814
- D3: WILSON, M.R.: "steroid transformation with fusarium oxysporum var. cubense and colletotrichum musae" STEROIDS, vol. 64, 1999, pages 834-843, XP002293815
- D4: CHALBOT, SONIA: "use of bioconversion for the preparation of 14-C labeled 7-alpha and 7-beta hydroxylated derivatives of dehydroepiandrosterone and epiandrosterone" STEROIDS, vol. 67, 2002, pages 1121-1127, XP002293816
- D5: KOLEK, TERESA: "biotransformation XLVII: transformation of 5-ene steroids in fusarium culmorum culture" THE JOURNAL OF STEROIDS BIOCHEMISTRY AND MOLECULAR BIOLOGY, vol. 71, 1999, pages 83-90, XP002293817
- D6: FR-A-2 771 105 (VITASTEROL) 21 May 1999 (1999-05-21)
- D7: US-A-2360447

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/IB2004/002078

2. Novelty and inventivity

2.1 Process to make 7-hydroxy-5-androstene steroids(claims 1,4,5)

Independent claim 1 and pending claims 4 and 5 are concerned with the process to make 7-hydroxy-5-androstene steroids by:

step 1: reacting a 5-androstene with microbial species of *Mucor* to undergo a microbial reaction leading to 7-hydroxy-5-androstene steroids.

step 2: isolating the 7-hydroxy-5-androstene steroids

2.11 Novelty

Document D1 disclose a process to make 7-hydroxy-5-androstene steroids (see page 341, fig. 1, compounds I-Id) via a microbial process using *Mucor piriformis*.

This document anticipate the subject matter of claim 1, since the Mucor used is not specified.

The subject-matter of claims 4 and 5 can be considered as novel since *Mucor rouxii* is used instead of *Mucor piriformis*.

2.12 Inventive step

Document D1 suggests that generally the *Mucor* species is useful for steroids transformation (page 339, left column, second paragraph), therefore the skilled person would expect that other type of *Mucor* could be used for the synthesis of 7-hydroxy-5-androstene steroids, therefore the subject matter of pending claims 4 and 5 cannot be considered as inventive.

In his letter of 16.11.2004, the Applicant mentionned that the yield of the process of D1 (page 340, col.1 and 2) is around 22%, it is not clear how the Applicant comes to this datas, we could not find any yield values in D1.

The Applicant argued that the claimed process leads to "good yields" and therefore provides an inventive step over D1.

No comparative tests have been provided.

In order to put forward inventive step, it is necessary (problem-solution approach) to

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.
PCT/IB2004/002078

provide comparative tests in similar experimental conditions.

2.2 Process to make 7-keto-5-androstene steroids (claims 2,3,6,7)

Pending claims 2,3,6 and 7 are concerned with the process to 7-keto-5-androstene steroids by:

step 1: reacting a 5-androstene with microbial species of *Mucor* to undergo a microbial reaction leading to 7-hydroxy-5-androstene steroids.

step 2: reacting the 7-hydroxy-5-androstene steroids with a specific bacterium leading to 7-keto-5-androstene steroids via an oxidation process.

step 3: isolating the 7-keto-5-androstene steroids

2.21 Novelty

None of the cited document in the search report (D1-D7) disclose a two step process starting with 5-androstene to make a 7-keto-5-androstene steroids via a 7-hydroxy-5-androstene steroids.

2.22 Inventivity

The second step of claim 2, namely reacting the 7-hydroxy-5-androstene steroids with a specific bacterium leading to 7-keto-5-androstene steroids via an oxidation process is generally known [see US2360447 (D7), first page, right column, lines 26-39].

The first step was also not recognised as inventive (see item 2.12).

So the subject matter of claims 2,3,6,7 cannot be considered as inventive.